

Probabilistic approach to a proliferation and migration dichotomy in the tumor cell invasion

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The proliferation and migration dichotomy of the tumor cell invasion is examined within a two-component continuous time random walk (CTRW) model. The balance equations for the cancer cells of two phenotypes with random switching between cell proliferation and migration are derived. The transport of tumor cells is formulated in terms of the CTRW with an arbitrary waiting time distribution law, while proliferation is modelled by a logistic growth. The overall rate of tumor cell invasion for normal diffusion and subdiffusion is determined.

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I. INTRODUCTION

One of the main features of malignant brain cancer is the ability of tumor cells to invade the normal tissue away from the multi-cell tumor core. Invasion of healthy tissue by a solid tumor (the core), and the role of oxygen and nutrient delivery have been the subject of extensive studies reflected in modern surveys, see e.g., [1]. Experimental data for a glioma cancer show that the proliferation rate of migratory cells is lower in the invasion region than in the core. It turns out that the proliferation and migration of cells are mutually exclusive: the high motility suppresses cell proliferation and vice versa. This phenomenon is known as the *migration-proliferation dichotomy* [2, 3]. The exact mechanism of switching between the two phenotypes of glioma cells is not known. There are several phenomenological models for this dichotomy. One can assume that the diffusion coefficient of cancer cells is a decreasing function of cell density [4]. As a result the cancer cell motility is greater in the invasion zone because of the small density of cells there. One can also assume the dependence of the proliferation term on cell density such that the proliferation rate increases with density [5]. An interesting dynamical model for the phenotype switch was suggested in [6]. However, this mathematical model involves many parameters, some of which are difficult to estimate. Recently the authors proposed a stochastic approach for the proliferation-migration switching that involves only two parameters [7]. The transport process was formulated in the framework of the continuous time random walk (CTRW) [8–10]. The main reason for employing the CTRW model was to give the mesoscopic description of cancer cell motility in terms of the random jump distribution and waiting times. One of the main purposes was to take into account anomalous transport (subdiffusion) leading to slow motility of cancer cells in the invasive zone. Among all possible cancer cell genotypes, leading to six main alternations of malignant growth [11], cell motility and invasion are most important for our consideration. The standard diffusion approximation for the transport (which is the parabolic limit of kinetics) together with a logistic growth yields an overestimation of the overall growth [12, 13]. Since the motility is the most critical feature of brain cancer, causing treatment failure, there is a need for a proper description of cancer cell motility beyond the standard diffusion approximation. In this connection, the hyperbolic limit of the multi-cellular microscopic system is important [14] to take into account cellular interaction in the description of macroscopic dynamics. A very interesting agent-based model was developed recently by Mansury and Deisboeck [15]. The transport process is described in terms of the local-search mechanism performed by tumor cells. The purpose of this “conscious” search is to find and then invade the most permissive location in extracellular matrix. A simplified scheme of migration–proliferation dichotomy in terms of CTRW was considered in [10, 16]. It involves two steps: cell fission with the characteristic time \mathcal{T}_f and cell transport with duration \mathcal{T}_t . During the time scale \mathcal{T}_f , the cells interact strongly and motility of the cells is small. During the time \mathcal{T}_t , interaction between the cells is weak and motility of the cells is determined by a “jump” length $\sim \mathcal{T}_t$.

Cell invasion is a very complex process controlled by matrix adhesion (see review [2]). It involves several steps including receptor-mediated adhesion of cells to extracellular matrix (ECM), matrix degradation by tumor-secreted proteases (proteolysis), detachment from ECM adhesion sites, and active invasion into intercellular space created by protease degradation. One of the purposes of this paper is to give a description of this complicated cell transport in terms of a non-symmetrical random walk model with memory effects. Chemotaxis and haptotaxis are taken into account by the biased random walk of cells that respond to external signals without alteration and migrate away from the tumor core. Matrix adhesion effects are modelled by using the heavy-tailed waiting time distributions that lead to subdiffusion of tumor cells.

II. TWO-COMPONENT CTRW WITH PROLIFERATION

A. Balance equations

In this paper we present a detailed analysis of the migration and proliferation of glioma cells in the framework of a two-component continuous time random walk with proliferation. The paper is an essential extension of our Letter [7] with new results and examples. Based on experimental observations of *migration-proliferation dichotomy*, we assume that the process of tumor cell invasion consists of two states. In state 1 (migratory phenotype) the cells randomly move but there is no cell proliferation. In state 2 (proliferating phenotype) the cancer cells do not migrate and only proliferation takes place. To describe the random switching between the two phenotypes, we employ the two-state Markov chain model. The cell of type 1 remains in state 1 during a waiting time τ_1 and then switches to a cell of type 2. After a waiting time τ_2 , spent in state 2, it switches back to a cell of type 1. Both waiting times τ_1 and τ_2 are mutually independent random variables exponentially distributed with parameters β_1 and β_2 :

$$\mathcal{P}(\tau_k) = \beta_k \exp(-\beta_k \tau_k) \quad k = 1, 2. \quad (1)$$

Here the parameters β_k are the switching rates, namely, β_1 is the switching rate from state 1 to 2, while β_2 determines the transition rate $2 \rightarrow 1$. Note that the generalization for the renovation processes with arbitrary probability densities for switching times is straightforward. An important feature of the present analysis is an observation of the influence of the migration-proliferation dichotomy on the overall invasion rate of cancer cells. In what follows we show how the overall propagation rate u depends on the parameters β_k .

We consider the growing tumor spheroid consisting of the tumor core with a high density of cells and the outer invasive zone where the cell density is much smaller. To describe the cancer cells of the two phenotypes we introduce the density of the cells of migrating phenotype, $n_1(t, \mathbf{x})$, and the density of the cells of proliferating phenotype, $n_2(t, \mathbf{x})$. The balance equations for $n_1(t, \mathbf{x})$ and $n_2(t, \mathbf{x})$ are

$$\begin{aligned} n_1(t, \mathbf{x}) = & n_1(0, \mathbf{x})\Psi(t)e^{-\beta_1 t} + \int_0^t \int_{R^d} n_1(t-s, \mathbf{x}-\mathbf{z})\Phi(s, \mathbf{z})e^{-\beta_1 s} d\mathbf{z} ds \\ & + \beta_2 \int_0^t n_2(t-s, \mathbf{x})\Psi(s)e^{-\beta_1 s} ds, \end{aligned} \quad (2)$$

$$\begin{aligned} n_2(t, \mathbf{x}) = & n_2(0, \mathbf{x})e^{-\beta_2 t} + \int_0^t f(n_1(t-s, \mathbf{x}), n_2(t-s, \mathbf{x})) e^{-\beta_2 s} ds \\ & + \beta_1 \int_0^t n_1(t-s, \mathbf{x})e^{-\beta_2 s} ds, \end{aligned} \quad (3)$$

where $\Phi(s, \mathbf{z})$ is the joint probability density function of making a jump \mathbf{z} in the time interval s to $s + ds$, and R_d denotes the integration is over d -dimensional space. The one dimensional case ($d = 1$) was considered in [7].

Cell migration (random jumps) involves a receptor-mediated adhesion to matrix proteins, matrix degradation by proteases, detachment from adhesion sites, active invasion into “new” intercellular space formed by degradation, etc. It would be extremely difficult to build up a rigorous deterministic model for this process. Since these factors are too many, we believe that a good alternative to such a model is a random walk with memory effects. The active mechanism of migration of tumor cells involves small random jumps and delay time between jumps. The latter might be of the same order as the proliferation time. This dynamics is obviously random and its distribution is given by the probability density function (pdf) $\psi(s)$:

$$\psi(s) = \int_{R^d} \Phi(s, \mathbf{z}) d\mathbf{z}, \quad (4)$$

where $\Phi(s, \mathbf{z})$ is the joint pdf.

Equation (2) is the conservation law for cells of type 1 at time t at position \mathbf{x} . The first term on the right hand side $n_1(0, \mathbf{x})\Psi(t)e^{-\beta_1 t}$ represents cells of type 1 that stay up to time t at position \mathbf{x} such that no jump occurred, and no switch took place. This term involves the function $\Psi(t)$

$$\Psi(t) = 1 - \int_0^t \psi(s) ds \quad (5)$$

which is the probability that a cell of type 1 makes no jump until time t . Note that the exponential factor

$$e^{-\beta_k t} = 1 - \int_0^t \mathcal{P}(\tau_k) ds, \quad k = 1, 2$$

is the probability that cells of phenotypes k do not switch until time t . The independence of the random jumps and switching gives us the probability $\Psi(t)e^{-\beta_1 t}$ while the first factor $n_1(0, \mathbf{x})$ is the initial density of cells of type 1 at \mathbf{x} .

The second term

$$\int_0^t \int_{R^d} n_1(t-s, \mathbf{x}-\mathbf{z}) \Phi(s, \mathbf{z}) e^{-\beta_1 s} d\mathbf{z} ds$$

gives us the number of cells of type 1 arriving at \mathbf{x} up to time t . We assume the following random mechanism of migration: the cell of type 1 at time $t-s$ at position $\mathbf{x}-\mathbf{z}$ waits a random time s before jumping a distance \mathbf{z} at position \mathbf{x} and remains a cell of type 1. The last term

$$\beta_2 \int_0^t n_2(t-s, \mathbf{x}) \Psi(s) e^{-\beta_1 s} ds$$

represents the number of cells of type 2 that switch to the cell of type 1 up to time t and remain the cells of type 1 (the factor $e^{-\beta_1 s}$). It also takes into account the fact that if transition $2 \rightarrow 1$ happens at time $t-s$, then no jump takes place during the remaining time s (the factor $\Psi(s)$).

Equation (3) describes the balance of cells of proliferating phenotype (no jumps). The first term on the right hand side, $n_2(0, \mathbf{x})e^{-\beta_2 t}$, is the density of cells of type 2 that stay up to time t at position \mathbf{x} such that no switch $2 \rightarrow 1$ takes place. The second term on the right hand side

$$\int_0^t f(n_1(t-s, \mathbf{x}), n_2(t-s, \mathbf{x})) e^{-\beta_2 s} ds$$

is the proliferation rate for cell of type 2, which occurs providing that no switch takes place up to time t . The last term

$$\beta_1 \int_0^t n_1(t-s, \mathbf{x}) e^{-\beta_2 s} ds \tag{6}$$

gives the number of cell of type 1 switching to the state 2 over the time interval $(0, t)$.

It is well known that the CTRW modelling is a standard technique for studying anomalous diffusion [8, 9]. We employ this technique to take into account subdiffusion that leads to slow motility of cancer cells in the invasive zone. In this paper each random step of a cancer cell is characterized by a waiting time s and a jump \mathbf{z} which are distributed according to the joint pdf $\Phi(s, \mathbf{z})$. This pdf can be written in a decoupled form

$$\Phi(s, \mathbf{z}) = \psi(s) \rho(\mathbf{z}), \tag{7}$$

where $\psi(s)$ is waiting time pdf and $\rho(\mathbf{z})$ is the pdf of cell jumps. This form corresponds to the case when the random waiting time and the individual displacement are independent. The subdiffusion regime occurs when the mean waiting time $\langle t \rangle = \int_0^\infty \tau \psi(\tau) d\tau$ is infinite and the spherically symmetrical pdf $\rho(|\mathbf{x}|) = \rho(r)$ has a finite variance $\sigma^2 = \int r^2 \rho(r) dr < \infty$, where r is the radius of the spheroid. If the asymptotic behavior for the waiting-time density $\psi(t)$ for large t is $t^{-1-\zeta}$ with $0 < \zeta < 1$, the mean waiting time $\langle t \rangle$ is infinite and the mean-square displacement $\sigma^2 t^\zeta$ corresponds to subdiffusion [8, 9]. When $\langle t \rangle$ is finite, there is normal diffusion: the mean-square displacement is Dt , where $D = \sigma^2/6 \langle t \rangle$ for the three-dimensional case ($d = 3$). Superdiffusion takes place when the variance σ^2 is infinite. Note that in many of the superdiffusion realization cases, the decoupling assumption of Eq. (7) can be inappropriate [17]. In what follows we consider only two regimes: normal diffusion and subdiffusion.

B. Integro-differential equations

The interesting feature of the balance equations (2) and (3) with $\Phi(s, \mathbf{z}) = \psi(s) \rho(\mathbf{z})$ is that they can be rewritten as a system of integro-differential equations:

$$\frac{\partial n_1}{\partial t} = \int_0^t \alpha(t-s) \int_{R^d} [n_1(s, \mathbf{x}-\mathbf{z}) - n_1(s, \mathbf{x})] \rho(\mathbf{z}) d\mathbf{z} ds - \beta_1 n_1 + \beta_2 n_2, \tag{8}$$

$$\frac{\partial n_2}{\partial t} = f(n_1, n_2) + \beta_1 n_1 - \beta_2 n_2, \quad (9)$$

where the memory kernel $\alpha(t)$ has to be determined. Let us derive these equations from (2) and (3) by using the Laplace transform for $\psi(t)$, and the Fourier transform for $\rho(\mathbf{x})$

$$\tilde{\psi}(H) = \mathcal{L}[\psi(t)] = \int_0^\infty \psi(t) e^{-Ht} dt, \quad \hat{\rho}(\mathbf{k}) = \mathcal{F}[\rho(\mathbf{x})] = \int_{R^d} \rho(\mathbf{x}) e^{i\mathbf{k} \cdot \mathbf{x}} d\mathbf{x} \quad (10)$$

and the Fourier-Laplace (F-L) transform for the densities $n_k(t, \mathbf{x})$

$$\hat{n}_k(H, \mathbf{k}) = \mathcal{FL}[n_k(t, \mathbf{x})] = \int_{R^d} \int_0^\infty n_k(t, \mathbf{x}) e^{-Ht + i\mathbf{k} \cdot \mathbf{x}} dt d\mathbf{x}, \quad k = 1, 2. \quad (11)$$

Equation (2) with $\Phi(s, \mathbf{z}) = \psi(s)\rho(\mathbf{z})$ in the F-L space reads

$$\begin{aligned} \hat{n}_1(H, \mathbf{k}) &= \hat{n}_1(0, \mathbf{k}) \frac{1 - \tilde{\psi}(H + \beta_1)}{H + \beta_1} + \hat{n}_1(H, \mathbf{k}) \hat{\rho}(\mathbf{k}) \tilde{\psi}(H + \beta_1) \\ &\quad + \beta_2 \hat{n}_2(H, \mathbf{k}) \frac{1 - \tilde{\psi}(H + \beta_1)}{H + \beta_1}. \end{aligned} \quad (12)$$

To perform the F-L transform in Eq. (11) we use the standard convolution property

$$\hat{n}_1(H, \mathbf{k}) \hat{\rho}(\mathbf{k}) \tilde{\psi}(H) = \int \int_0^\infty \left[\int_0^t \int n_1(t-s, \mathbf{x}-\mathbf{z}) \rho(\mathbf{z}) \psi(s) d\mathbf{z} ds \right] e^{-Ht + i\mathbf{k} \cdot \mathbf{x}} dt d\mathbf{x}.$$

Rearranging Eq. (12) and introducing the ‘memory’ kernel $\alpha(t)$ in term of its Laplace transform:

$$\tilde{\alpha}(H) = \frac{(H + \beta_1) \tilde{\psi}(H + \beta_1)}{(1 - \tilde{\psi}(H + \beta_1))}, \quad (13)$$

we obtain

$$H \hat{n}_1(H, \mathbf{k}) - \hat{n}_1(0, \mathbf{k}) = \hat{n}_1(H, \mathbf{k}) \tilde{\alpha}(H) (\hat{\rho}(\mathbf{k}) - 1) + \beta_2 \hat{n}_2(H, \mathbf{k}) - \beta_1 \hat{n}_1(H, \mathbf{k}). \quad (14)$$

Applying the F-L transform inversion to Eq. (14), we obtain the integro-differential equation (8). To find the F-L transform of Eq. (3), we denote the nonlinear proliferation term by $Z(t, \mathbf{x}) = f(n_1(t, \mathbf{x}), n_2(t, \mathbf{x}))$. Its F-L transform is

$$\hat{Z}(H, \mathbf{k}) = \mathcal{LF}[Z(t, \mathbf{x})]. \quad (15)$$

We have from Eq. (3)

$$\hat{n}_2(H, \mathbf{k}) = \hat{n}_2(0, \mathbf{k}) \frac{1}{H + \beta_2} + \hat{Z}(H, \mathbf{k}) \frac{1}{H + \beta_2} + \beta_1 \hat{n}_1(H, \mathbf{k}) \frac{1}{H + \beta_2}, \quad (16)$$

where $\hat{Z}(H, \mathbf{k})/(H + \beta_2) = \mathcal{LF} \int_0^t Z(t-s, \mathbf{x}) e^{-\beta_2 s} ds$. Rearranging Eq. (16) in the following form

$$H \hat{n}_2(H, \mathbf{k}) - \hat{n}_2(0, \mathbf{k}) = \hat{Z}(H, \mathbf{k}) + \beta_1 \hat{n}_1(H, \mathbf{k}) - \beta_2 \hat{n}_2(H, \mathbf{k}),$$

and applying the F-L inversion and using Eq. (15), we obtain Eq. (9).

C. Probability density function for cell jumps

Now we are in a position to discuss different approximations for the probability density function for cell jumps $\rho(\mathbf{z})$. Of course this function is not symmetrical in general. The cells of the migrating phenotype are biased to migrate away from the tumor spheroid core. The reasons for this asymmetrical creeping are the non-uniform nutrient concentration (chemotaxis), the gradient of cell adhesion sites (haptotaxis), etc. Experimental observations suggest that cell jumps

are controlled by adhesion of tumor cells to extracellular matrix and jump lengths are very small [2]. Therefore $\rho(\mathbf{z})$ is a rapidly decaying function for large $|\mathbf{z}|$. In other words, the density of tumor cells varies on the scales that are much larger than the typical jump length. Thus one can use the Taylor series in Eq. (2) with $\Phi(s, \mathbf{z}) = \psi(s)\rho(\mathbf{z})$ expanding $n_1(t-s, \mathbf{x}-\mathbf{z})$ in \mathbf{z} and truncate the series at the 2nd moment. This truncation for rapidly decaying function $\rho(\mathbf{z})$ is a well defined procedure, since the higher moments become progressively smaller [18]. We have

$$\int_{R^d} n_1(t-s, \mathbf{x}-\mathbf{z})\rho(\mathbf{z})d\mathbf{z} = n_1(t-s, \mathbf{x}) - \langle z_i \rangle \frac{\partial n_1}{\partial x_i} + \frac{1}{2} \langle z_i z_j \rangle \frac{\partial^2 n_1}{\partial x_i \partial x_j} + \dots, \quad (17)$$

where the Einstein rule for summation over repeated indices i and j is implied, and angular brackets denote averaging with respect to $\rho(\mathbf{z})$:

$$\langle z_i \rangle = \int_{R^d} z_i \rho(\mathbf{z}) d\mathbf{z}, \quad \langle z_i z_j \rangle = \int_{R^d} z_i z_j \rho(\mathbf{z}) d\mathbf{z}. \quad (18)$$

Substitution of Eq. (17) into Eq. (2) with the decouple property $\Phi(s, \mathbf{z}) = \psi(s)\rho(\mathbf{z})$ yields

$$\begin{aligned} n_1(t, \mathbf{x}) &= n_1(0, \mathbf{x})\Psi(t)e^{-\beta_1 t} + \int_0^t n_1(t-s, \mathbf{x})\psi(s)e^{-\beta_1 s} ds - \langle z_i \rangle \int_0^t \frac{\partial n_1}{\partial x_i} \psi(s)e^{-\beta_1 s} ds \\ &+ \frac{1}{2} \langle z_i z_j \rangle \int_0^t \frac{\partial^2 n_1}{\partial x_i \partial x_j} \psi(s)e^{-\beta_1 s} ds + \beta_2 \int_0^t n_2(t-s, \mathbf{x})\Psi(s)e^{-\beta_1 s} ds. \end{aligned} \quad (19)$$

Note that the third term on the right hand side of this equation reflects a bias of random walk in the direction $\langle \mathbf{z} \rangle$. In fact, this equation involves the first two moments for random jumps: $\langle z_i \rangle$ and $\langle z_i z_j \rangle$. It can be rewritten as the integro-differential equation

$$\frac{\partial n_1}{\partial t} + \langle z_i \rangle \int_0^t \alpha(t-s) \frac{\partial n_1}{\partial x_i} ds = \frac{1}{2} \langle z_i z_j \rangle \int_0^t \alpha(t-s) \frac{\partial^2 n_1}{\partial x_i \partial x_j} ds - \beta_1 n_1 + \beta_2 n_2. \quad (20)$$

If the cell jumps are normally distributed then the characteristic function of $\rho(\mathbf{z})$ is

$$\hat{\rho}(\mathbf{k}) = \exp \left(i a_i k_i - \frac{1}{2} \sigma_{ij} k_i k_j \right), \quad (21)$$

where the summation convection is implied for the repeated index. The positive definite matrix σ_{ij} can be written in terms of the first two moments

$$\sigma_{ij} = \langle z_i z_j \rangle - \langle z_i \rangle \langle z_j \rangle. \quad (22)$$

The probability density function $\rho(\mathbf{z})$ is

$$\rho(\mathbf{z}) = \frac{1}{(2\pi)^{d/2} (\det \sigma)^{1/2}} \exp \left(-\frac{1}{2} (\sigma^{-1})_{ij} (z_i - \langle z_i \rangle) (z_j - \langle z_j \rangle) \right), \quad (23)$$

where $(\sigma^{-1})_{ij}$ is an inverse matrix. If we assume that there is no bias, $\langle z_j \rangle = 0$, and $\langle z_i z_j \rangle = 0$ for $i \neq j$, and $\langle z_i^2 \rangle = \frac{\langle z^2 \rangle}{d} = \frac{\sigma^2}{d}$. Then Eq. (19) takes the form

$$\begin{aligned} n_1(t, \mathbf{x}) &= n_1(0, \mathbf{x})\Psi(t)e^{-\beta_1 t} + \int_0^t n_1(t-s, \mathbf{x})\psi(s)e^{-\beta_1 s} ds \\ &+ \frac{\sigma^2}{2d} \int_0^t \Delta n_1(t-s, \mathbf{x})\psi(s)e^{-\beta_1 s} ds + \beta_2 \int_0^t n_2(t-s, \mathbf{x})\Psi(s)e^{-\beta_1 s} ds. \end{aligned} \quad (24)$$

From the last equation one obtains integro-differential equation for n_1 in d dimension

$$\frac{\partial n_1}{\partial t} = \frac{\sigma^2}{2d} \int_0^t \alpha(t-s) \Delta n_1(s, \mathbf{x}) ds - \beta_1 n_1 + \beta_2 n_2. \quad (25)$$

Note that the one-dimensional case ($d = 1$) was analyzed in [7].

D. Memory kernel and waiting time probability density function

The formula

$$\tilde{\alpha}(H) = \frac{(H + \beta_1) \tilde{\psi}(H + \beta_1)}{1 - \tilde{\psi}(H + \beta_1)} \quad (26)$$

gives us the relationship between the transport memory kernel $\alpha(t)$ in (20) and the waiting-time pdf $\psi(t)$ in terms of their Laplace transforms. It should be emphasized that it is impossible to find an explicit expression for the memory kernel $\alpha(t)$ for arbitrary choices of the waiting-time pdf $\psi(t)$. However, we are concerned with the rate of the spreading of tumor cells. In what follows we show that this rate depends on the Laplace transform $\tilde{\alpha}(H)$ rather than $\alpha(t)$. That is why the formula (26) is so important for our analysis. It follows from (26) that the transport kernel $\alpha(t)$ depends on the parameter β_1 . This means that we can not separate the transport process and random switching in general. This phenomenon has been discussed recently in the literature on anomalous transport with reactions [19, 20].

Let us consider three typical distributions for the waiting-time pdf $\psi(t)$.

(i) *Exponential distribution.* The random waiting time is exponentially distributed if it has a density

$$\psi(t) = \lambda e^{-\lambda t}. \quad (27)$$

The Laplace transform for this distribution is

$$\tilde{\psi}(H) = \int_0^\infty \lambda e^{-\lambda t} e^{-Ht} dt = \frac{\lambda}{\lambda + H} \quad (28)$$

and

$$\tilde{\alpha}(H) = \frac{(H + \beta_1) \tilde{\psi}(H + \beta_1)}{(1 - \tilde{\psi}(H + \beta_1))} = \lambda; \quad (29)$$

therefore $\alpha(t) = \lambda \delta(t)$. In this case the kernel $\alpha(t)$ is independent of β_1 . Thus we have a classical system of convection-diffusion-reaction equations

$$\frac{\partial n_1}{\partial t} + v_i \frac{\partial n_1}{\partial x_i} = D_{ij} \frac{\partial^2 n_1}{\partial x_i \partial x_j} - \beta_1 n_1 + \beta_2 n_2, \quad (30)$$

$$\frac{\partial n_2}{\partial t} = f(n_1, n_2) + \beta_1 n_1 - \beta_2 n_2, \quad (31)$$

with the diffusion tensor $D_{ij} = \lambda \langle z_i z_j \rangle / 2$ and the velocity $\mathbf{v} = \lambda \langle \mathbf{z} \rangle$.

(ii) *Gamma distribution.* The waiting-time pdf $\psi(t)$ corresponds to the family of gamma distributions with parameters m and λ :

$$\psi(t) = \frac{\lambda^m t^{m-1} e^{-\lambda t}}{\Gamma(m)}. \quad (32)$$

Then $\tilde{\psi}(H) = \left(\frac{\lambda}{\lambda + H} \right)^m$ and

$$\tilde{\alpha}(H) = \frac{(H + \beta_1) \lambda^m}{(\lambda + H + \beta_1)^m - \lambda^m}. \quad (33)$$

For example, if $m = 2$

$$\tilde{\alpha}(H) = \frac{\lambda^2}{2\lambda + H + \beta_1}, \quad (34)$$

and the memory kernel is

$$\alpha(t) = \lambda^2 e^{-(2\lambda + \beta_1)t}. \quad (35)$$

The main result here is that the transport memory kernel depends on the parameter β_1 . The integro-differential equation for cells of migratory phenotype takes the form

$$\frac{\partial n_1}{\partial t} + v_i \lambda \int_0^t e^{-(2\lambda + \beta_1)s} \frac{\partial n_1}{\partial x_i} ds = D_{ij} \lambda \int_0^t e^{-(2\lambda + \beta_1)s} \frac{\partial^2 n_1}{\partial x_i \partial x_j} ds - \beta_1 n_1 + \beta_2 n_2. \quad (36)$$

The integro-differential Eq. (36) can be rewritten as the hyperbolic reaction-transport equation, and corresponding travelling wave solutions can be found as in [21, 22] (see also [14]).

(iii) *Power law waiting time distribution.* The power law $\psi(t) \sim 1/(1+t/\tau)^{1+\gamma}$ with $0 < \gamma < 1$ is used in many applications [9]. Here we use τ which is (in general case) not equal to $1/\lambda$ to stress the fractional property of cell dynamics. It is more convenient to use its Laplace transform

$$\tilde{\psi}(H) = \frac{1}{1 + (H\tau)^\gamma}. \quad (37)$$

Then

$$\tilde{\alpha}(H) = \frac{(H + \beta_1) \tilde{\psi}(H + \beta_1)}{(1 - \tilde{\psi}(H + \beta_1))} = \frac{(H + \beta_1)^{1-\gamma}}{\tau^\gamma}. \quad (38)$$

III. CANCER SPREADING RATE

The overall rate u at which cancer cells spread is usually defined as the velocity of the experimentally detectable tumor front. In the generic Fisher equation setting the propagation rate is $u = 2\sqrt{DU}$, where D is the diffusion coefficient and U is the proliferation rate [18]. The speed of this front is determined by the processes taking place at the leading edge of the cells' profile. In this paper we have a system of equations (2) and (3) and we define the overall spreading rate as the speed of the travelling wave solution of this system. For front-like initial conditions, the fronts for both densities n_1 and n_2 quickly achieve the stationary forms that propagate with a constant rate u . The main purpose here is to find the dependence of this propagation rate on the statistical characteristics of the random switching process, β_1 and β_2 , two moments for random jumps: $\langle z_i \rangle$ and $\langle z_i z_j \rangle$ and waiting time distribution $\psi(t)$. We use the logistic growth for cell proliferation

$$f(n_1, n_2) = U n_2 (1 - (n_1 + n_2)/K), \quad (39)$$

where U is the cell proliferation rate and K is the carrying capacity of the environment. We assume that the initial tumor spheroid of radius R has the following distribution of cells

$$n_k(0, \mathbf{x}) = \begin{cases} A_k & \text{if } \sum_{i=1}^d x_i^2 \leq R^2, \\ 0 & \text{otherwise,} \end{cases} \quad (40)$$

where positive constant A_1 and A_2 represent the stable equilibrium points of the densities n_1 and n_2 . They can be found from two equations $A_1 + A_2 = K$ and $\beta_1 A_1 = \beta_2 A_2$:

$$A_1 = \frac{\beta_2 K}{\beta_1 + \beta_2}, \quad A_2 = \frac{\beta_1 K}{\beta_1 + \beta_2}. \quad (41)$$

We assume that the characteristic length scale for the tumor front is much smaller than the radius of the initial tumor spheroid. We also assume that the bias acts in the radial direction such that $\langle \mathbf{z} \rangle = \langle r \rangle \mathbf{e}_r$. These assumptions allow us to consider the propagation of the effective plane front in the radial direction, neglecting all curvature effects. We expect that the long time development leads to the propagation of travelling fronts of permanent forms: $n_1(r - ut)$ and $n_2(r - ut)$, where the rate u is common to both densities n_1 and n_2 .

The balance equations for densities n_1 and n_2 are of the form

$$\begin{aligned} n_1(t, r) = & n_1(0, r) \Psi(t) e^{-\beta_1 t} + \int_0^t n_1(t-s, r) \psi(s) e^{-\beta_1 s} ds - \langle r \rangle \int_0^t \frac{\partial n_1}{\partial r} \psi(s) e^{-\beta_1 s} ds \\ & + \frac{\sigma^2}{2d} \int_0^t \frac{\partial^2 n_1}{\partial r^2} \psi(s) e^{-\beta_1 s} ds + \beta_2 \int_0^t n_2(t-s, r) \Psi(s) e^{-\beta_1 s} ds, \end{aligned} \quad (42)$$

$$\begin{aligned}
n_2(t, r) = & n_2(0, r)e^{-\beta_2 t} + U \int_0^t n_2(t-s, r)(1 - (n_1(t-s, r) + n_2(t-s, r)) / K)e^{-\beta_2 s} ds \\
& + \beta_1 \int_0^t n_1(t-s, r)e^{-\beta_2 s} ds.
\end{aligned} \tag{43}$$

This system of equations is a starting point for the analysis of plane front propagation in a radial direction.

A. Hyperbolic scaling and Hamilton-Jacobi equation

The objective here is to find the rate u without resolving the shape of the travelling waves [12, 23]. For this purpose we use a hyperbolic scaling $r \rightarrow r/\varepsilon$, $t \rightarrow t/\varepsilon$ and the rescaled density $n_k^\varepsilon(t, r) = n_k(t/\varepsilon, r/\varepsilon)$ (see Appendix A). We write the density $n_k^\varepsilon(t, r)$ in the exponential form

$$n_k^\varepsilon(t, r) = A_k \exp\left(-\frac{G^\varepsilon(t, r)}{\varepsilon}\right), \quad k = 1, 2 \tag{44}$$

where the non-negative function $G^\varepsilon(t, r)$ describes the logarithmic asymptotic of both densities and plays a very important role. It follows from (44) that as long as the function

$$G(t, r) = \lim_{\varepsilon \rightarrow 0} G^\varepsilon(t, r) \tag{45}$$

is positive, the rescaled density $n_k^\varepsilon(t, r) \rightarrow 0$ as $\varepsilon \rightarrow 0$. We may argue that the equation $G(t, r(t)) = 0$ gives us the spreading front position $r(t)$ in the long-time and large-distance limit [12]. Substitution of the exponential transformation (44) into the equations for the rescaled densities $n_i^\varepsilon(t, r)$ and taking the limit $\varepsilon \rightarrow 0$ yield two equations for A_1 and A_2 . These equations have a non-trivial solution when the corresponding determinant is equal to zero (see Appendix A). It gives the following equation for $G(t, r)$:

$$\begin{aligned}
& \left[1 - \left(1 + \langle r \rangle \frac{\partial G}{\partial r} + \frac{\sigma^2}{2d} \left(\frac{\partial G}{\partial r}\right)^2\right) \int_0^\infty e^{\frac{\partial G}{\partial t} s} \psi(s) e^{-\beta_1 s} ds\right] \left[1 - U \int_0^\infty e^{\frac{\partial G}{\partial t} s} e^{-\beta_2 s} ds\right] \\
& - \beta_1 \beta_2 \int_0^\infty e^{\frac{\partial G}{\partial t} s} \Psi(s) e^{-\beta_1 s} ds \times \int_0^\infty e^{\frac{\partial G}{\partial t} s} e^{-\beta_2 s} ds = 0.
\end{aligned} \tag{46}$$

In terms of the Laplace transform $\tilde{\psi}(H) = \mathcal{L}[\psi(t)]$, Eq. (46) can be rewritten as a generalized Hamilton-Jacobi equation

$$1 - \left(1 + \langle r \rangle \frac{\partial G}{\partial r} + \frac{\sigma^2}{2d} \left(\frac{\partial G}{\partial r}\right)^2\right) \tilde{\psi}\left(-\frac{\partial G}{\partial t} + \beta_1\right) = \frac{\beta_1 \beta_2 (1 - \tilde{\psi}(-\frac{\partial G}{\partial t} + \beta_1))}{(-\frac{\partial G}{\partial t} + \beta_1)(-\frac{\partial G}{\partial t} + \beta_2 - U)}. \tag{47}$$

Note that inferring Eq. (47), we do not make any assumptions regarding waiting time pdf $\psi(s)$.

B. Wavefront velocity

Let us introduce the Hamiltonian function H and the generalized momentum p

$$H = -\frac{\partial G}{\partial t}, \quad p = \frac{\partial G}{\partial r}. \tag{48}$$

Then Hamilton-Jacobi equation (47) takes the form of the quadratic equation:

$$\langle r \rangle p + \frac{\sigma^2 p^2}{2d} - \frac{1}{\tilde{\psi}(H + \beta_1)} \left[1 - \frac{\beta_1 \beta_2 (1 - \tilde{\psi}(H + \beta_1))}{(H + \beta_1)(H + \beta_2 - U)}\right] + 1 = 0. \tag{49}$$

This equation is very important because it allows us to find the spreading rate u

$$u = \frac{\partial H}{\partial p} = \frac{H}{p(H)}. \tag{50}$$

We may equivalently write $u = \min_H \left\{ \frac{H}{p(H)} \right\}$, so $u = \frac{H}{p(H)}$, where H can be found from equation

$$\frac{\partial p}{\partial H} = \frac{p(H)}{H} \quad (51)$$

Let us illustrate this formula by using the classical Fisher equation

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} + Un(1-n)$$

for which the Hamiltonian is $H = Dp^2/2 + U$. Using this expression, we obtain

$$p(H) = \left(\frac{2H - 2U}{D} \right)^{1/2}. \quad (52)$$

From Eqs. (51) and (52) we obtain $H = Dp^2(H) = 2U$, and therefore, the spreading rate for the Fisher equation is $u_F = H/p(H) = 2(DU)^{1/2}$. This is the classical propagation speed.

In what follows we consider a case when the mean jump length in the radial direction is zero, $\langle r \rangle = 0$. If the random waiting time is exponentially distributed (27): $\psi(t) = \lambda e^{-\lambda t}$, then the equation for the migratory cells is

$$\frac{\partial n_1}{\partial t} = D \frac{\partial^2 n_1}{\partial r^2} - \beta_1 n_1 + \beta_2 n_2. \quad (53)$$

The momentum $p(H)$ can be found from (49)

$$p^2 = \frac{(H + \beta_1)}{D} - \frac{\beta_1 \beta_2}{D(H + \beta_2 - U)}. \quad (54)$$

If we assume that $\beta_1 = \beta_2$, we can find from (50) that $H = U$ and (54) $p = (U/D)^{1/2}$, and $H = U$. Therefore, the spreading rate is $u_0 = (UD)^{1/2}$ which is half of the classical Fisher-KPP (Fisher-Kolmogorov-Petrovskii-Piskunov) propagation speed u_F . This result shows that the propagation rate is independent of the random migration-proliferation switching for $\beta_1 = \beta_2$. When $\beta_1 \neq \beta_2$ one can find the ratio of the propagation rate u and $u_0 = (UD)^{1/2}$ as

$$\left(\frac{u}{u_0} \right)^2 = \frac{4(H + \beta_2 - U)^3 [(H + \beta_2 - U)(H + \beta_1) - \beta_1 \beta_2]}{[(H + \beta_2 - U)^2 + \beta_1 \beta_2]^2}, \quad (55)$$

where H is determined by Eq. (51). For the fixed values of β_1 and U , the wavefront propagation rate versus β_2/β_1 is depicted in Fig. 1.

For the power law distribution $\psi(t) \sim (\tau/t)^{1+\gamma}$ with $0 < \gamma < 1$, the mean waiting time is divergent: $\langle t \rangle = \infty$. This assumption alone leads to the temporal fractional differential operator and corresponding anomalous diffusion equation [9]. The mean squared displacement for mobile cells is

$$\langle r^2(t) \rangle = \frac{4D_\gamma}{\Gamma(1+\gamma)} t^\gamma, \quad (56)$$

where $D_\gamma = \sigma^2/2d\tau^\gamma$.

Let us find the overall propagation of cancer cells as a result of interaction of subdiffusion (56), logistic proliferation (39), and random migration-proliferation switching (1). For the Laplace transform $\tilde{\psi}(H) = (1 + (H\tau)^\gamma)^{-1}$, the momentum $p(H)$ can be found from (49):

$$p^2 = \frac{(H + \beta_1)^\gamma}{D_\gamma} - \frac{\beta_1 \beta_2 (H + \beta_1)^{\gamma-1}}{D_\gamma (H + \beta_2 - U)}. \quad (57)$$

This formula together with (50) allows us to find the overall propagation rate of tumor cells u_γ for the subdiffusion case. The case $\gamma = 1$ corresponds to normal diffusion. One can find from (50), (54) and (57) the ratio of the anomalous propagation rate u_γ and the normal rate u determined by (55):

$$\frac{u_\gamma}{u} = (H_\gamma \tau + \beta_1 \tau)^{\frac{1-\gamma}{2}}. \quad (58)$$

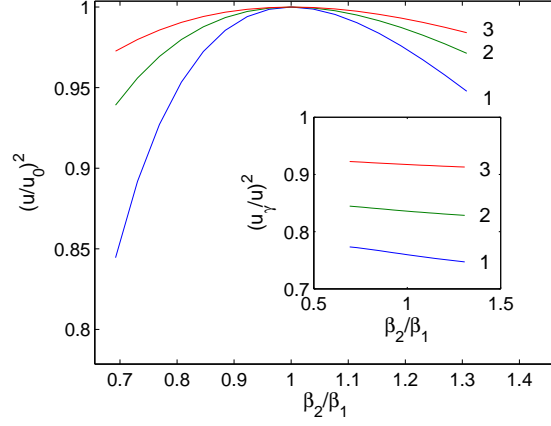


Figure 1: (Color online) Propagation speed $(u/u_0)^2$ vs β_2/β_1 . The values of $\beta_1/U = [3, 4.5, 6.5]$ correspond to plots (1), (2), and (3), respectively. The insert corresponds to a solution of Eqs. (57) and (58) for the same values of β_1/U and $\gamma = 0.7$.

Since the “microscopic” time τ is much smaller than the characteristic “cell proliferation” time U^{-1} and switching time β_1^{-1} and $H_\gamma \sim U$, we conclude that $H\tau + \beta_1\tau < 1$. This condition of $H \sim U$ is also confirmed by numerical solutions of Eqs. (51), (54), (57), and (58) (see insert in Fig. 1). It follows from (58) that the ratio u_γ/u increases up to 1 with γ in the interval $0 < \gamma < 1$. This means that normal diffusion leads to overestimation of the overall cancer spreading. Note that the advantage of balance Eqs. (2) and (3) is that they are related to a “mesoscopic” description of migratory cancer cells, and give us the statistical meaning of the phenomenological reaction-transport equation (20).

IV. REACTION-TRANSPORT EQUATIONS

The influence of the migration-proliferation dichotomy on the overall propagation rate is an important factor in glioma development. The Markovian switching between two phenotypes described by Eq. (1) can be generalized for the case when memory effects are taken into account. The system of integro-differential equations (8) and (9) takes the form

$$\begin{aligned} \frac{\partial n_1}{\partial t} = & \int_0^t \alpha(t-s) \int_{R^d} [n_1(s, \mathbf{x} - \mathbf{z}) - n_1(s, \mathbf{x})] \rho(\mathbf{z}) d\mathbf{z} ds \\ & + \int_0^t [\mu_2(t-s)n_2(s, \mathbf{x}) - \mu_1(t-s)n_1(s, \mathbf{x})] ds, \end{aligned} \quad (59)$$

$$\frac{\partial n_2}{\partial t} = f(n_1, n_2) - \int_0^t [\mu_2(t-s)n_2(s, \mathbf{x}) - \mu_1(t-s)n_1(s, \mathbf{x})] ds, \quad (60)$$

where $\mu_i(t)$ is the memory kernel for non-Markovian switching. Combining Eqs. (59) and (60) one finds that a total density $n = n_1 + n_2$ obeys the equation

$$\frac{\partial n}{\partial t} = \int_0^t \alpha(t-s) \int_{R^d} [n(s, \mathbf{x} - \mathbf{z}) - n(s, \mathbf{x})] \rho(\mathbf{z}) d\mathbf{z} ds + f(n_1, n_2). \quad (61)$$

This equation does not restrict any possible random transitions between migration and proliferation phenotypes. Moreover, it can be a starting point of the glioma modelling in the framework of the differential equations. It can be rewritten in terms of the total density alone, if we introduce the probabilities p_j such that $n_1 = p_1 n$ and $n_2 = p_2 n$. By using the logistic growth for cell proliferation $f(n_1, n_2) \equiv f(n_2) = U n_2 (1 - n_2/K)$ and rescaling $p_2 n \rightarrow n$, we obtain

$$\frac{\partial n}{\partial t} = p_1 \int_0^t \alpha(t-s) \int_{R^d} [n(s, \mathbf{x} - \mathbf{z}) - n(s, \mathbf{x})] \rho(\mathbf{z}) d\mathbf{z} ds + U p_2 n (1 - n/K). \quad (62)$$

Let us find these probabilities for Markovian switching (1). In fact there are four characteristic times in our model: proliferation time (U^{-1} for logistic growth), the transport time $\langle t \rangle = \int_0^\infty t\psi(t)dt$ (averaging waiting time), and two switching times β_1^{-1} and β_2^{-1} . If we assume that both switching times are small compared to the growth time U^{-1} and transport time $\langle t \rangle$, the “fast” switching process can be averaged. The “fast” local dynamics of densities n_1 and n_2 governed by the equations

$$\frac{\partial n_1}{\partial t} = -\beta_1 n_1 + \beta_2 n_2, \quad \frac{\partial n_2}{\partial t} = \beta_1 n_1 - \beta_2 n_2. \quad (63)$$

The solution for any \mathbf{x} is

$$n_1(t) = \frac{\beta_2}{\beta_1 + \beta_2} + \left[n_1(0) - \frac{\beta_2}{\beta_1 + \beta_2} \right] e^{-(\beta_1 + \beta_2)t}, \quad (64)$$

$$n_2(t) = \frac{\beta_1}{\beta_1 + \beta_2} + \left[n_2(0) - \frac{\beta_1}{\beta_1 + \beta_2} \right] e^{-(\beta_1 + \beta_2)t}. \quad (65)$$

For the large intermediate time T such that $\beta_1^{-1} \sim \beta_2^{-1} \ll T \ll U^{-1}$, we have a local equilibrium, that is, $n_1 = \frac{\beta_2}{\beta_1 + \beta_2}$ and $n_2 = \frac{\beta_1}{\beta_1 + \beta_2}$. If we consider now the transport and proliferation, it is clear that the total number of cancer cells n splits locally to $\frac{\beta_2}{\beta_1 + \beta_2}n$ of migrating phenotype and $\frac{\beta_1}{\beta_1 + \beta_2}n$ of proliferating phenotype. So

$$n_1(t, \mathbf{x}) = \frac{\beta_2}{\beta_1 + \beta_2} n(t, \mathbf{x}), \quad n_2(t, \mathbf{x}) = \frac{\beta_1}{\beta_1 + \beta_2} n(t, \mathbf{x}). \quad (66)$$

This means that we have only one variable $n(t, \mathbf{x})$ for which we can formulate a balance equation considering the transport for $n_1(t, \mathbf{x})$ and proliferation for $n_2(t, \mathbf{x})$. The probabilities are

$$p_1 = \frac{\beta_2}{\beta_1 + \beta_2}, \quad p_2 = \frac{\beta_1}{\beta_1 + \beta_2}. \quad (67)$$

In this limiting case, the model can be formulated in terms of the linear balance equation for the total number of cancer cells per unit volume $n(t, \mathbf{x})$

$$n(t, \mathbf{x}) = \frac{\beta_2}{\beta_1 + \beta_2} \int_0^t \int_{R^d} n(t-s, \mathbf{x}-\mathbf{z}) \psi(s) \rho(\mathbf{z}) d\mathbf{z} ds + \frac{\beta_1}{\beta_1 + \beta_2} U \int_0^t n(t-s, \mathbf{x}) ds. \quad (68)$$

This reaction-transport equation can be also used to study the wavefront propagation in the framework of the Hamiltonian-Jacobi approach.

V. CONCLUSION

We developed a probabilistic approach for a *migration-proliferation dichotomy* in the spreading of tumor cells in the invasive zone. We derived the balance equations for densities of cancer cells of two phenotypes. In the migratory state the cells randomly move but there is no cell proliferation, while in the proliferating state the cancer cells do not migrate and only proliferation takes place. We took into account random switching between cell proliferation and migration by using a two-state Markov chain. The transport of tumor cells is formulated in terms of the CTRW with an arbitrary waiting time distribution, while proliferation is modeled by a non-linear function of both densities. We found the overall rate of tumor cell invasion for both normal diffusion and subdiffusion. The advantage of our probabilistic approach is that it allows us to take into account anomalous (subdiffusive) transport within the general scheme of migration, proliferation, and phenotype switching. We showed the equivalence of balance equations to a system of integro-differential equations involving memory effects for the transport of mobile cells. By using a hyperbolic scaling and Hamilton-Jacobi formalism we derived formulae for the overall spreading rate of cancer cells. We showed that the memory effects (subdiffusion) leads to a decrease in propagation rate compared to a standard diffusion approximation for transport.

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Appendix A

Rescaling of Eqs. (42) and (43), we obtain

$$\begin{aligned}
n_1^\varepsilon(t, r) &= n_1^\varepsilon(0, r)\Psi(t)e^{-\beta_1 t/\varepsilon} + \int_0^{t/\varepsilon} n_1^\varepsilon(t - \varepsilon s, r)\psi(s)e^{-\beta_1 s} ds \\
&\quad -\varepsilon < r > \int_0^{t/\varepsilon} \frac{\partial n_1^\varepsilon}{\partial r} \psi(s)e^{-\beta_1 s} ds + \frac{\varepsilon^2 \sigma^2}{2d} \int_0^{t/\varepsilon} \frac{\partial^2 n_1^\varepsilon}{\partial r^2} (t - \varepsilon s, r)\psi(s)e^{-\beta_1 s} ds \\
&\quad + \beta_2 \int_0^{t/\varepsilon} n_2^\varepsilon(t - \varepsilon s, r)\Psi(s)e^{-\beta_1 s} ds,
\end{aligned} \tag{69}$$

$$\begin{aligned}
n_2^\varepsilon(t, r) &= n_2^\varepsilon(0, r)e^{-\beta_2 t/\varepsilon} + U \int_0^{t/\varepsilon} n_2^\varepsilon(t - \varepsilon s, r)(1 - (n_1^\varepsilon + n_2^\varepsilon)/K)e^{-\beta_2 s} ds \\
&\quad + \beta_1 \int_0^{t/\varepsilon} n_1^\varepsilon(t - \varepsilon s, r)e^{-\beta_2 s} ds.
\end{aligned} \tag{70}$$

Substitution of the exponential transformation $n_k^\varepsilon(t, r) = A_k \exp\left(-\frac{G^\varepsilon(t, r)}{\varepsilon}\right)$ into these equations and accounting initial conditions yields

$$\begin{aligned}
A_1 &= A_1 \int_0^{t/\varepsilon} \exp\left[\frac{G^\varepsilon(t, r) - G^\varepsilon(t - \varepsilon s, r)}{\varepsilon}\right] \psi(s)e^{-\beta_1 s} ds \\
-\varepsilon < r > A_1 \exp\left(\frac{G^\varepsilon(t, r)}{\varepsilon}\right) \int_0^{t/\varepsilon} \frac{\partial}{\partial r} \exp\left(-\frac{G^\varepsilon(t - \varepsilon s, r)}{\varepsilon}\right) \psi(s)e^{-\beta_1 s} ds \\
&\quad + \frac{\varepsilon^2 \sigma^2 A_1}{2d} \exp\left(\frac{G^\varepsilon(t, r)}{\varepsilon}\right) \int_0^{t/\varepsilon} \frac{\partial^2}{\partial r^2} \exp\left(-\frac{G^\varepsilon(t - \varepsilon s, r)}{\varepsilon}\right) \psi(s)e^{-\beta_1 s} ds \\
&\quad + \beta_2 A_2 \int_0^{t/\varepsilon} \exp\left[\frac{G^\varepsilon(t, r) - G^\varepsilon(t - \varepsilon s, r)}{\varepsilon}\right] \Psi(s)e^{-\beta_1 s} ds,
\end{aligned} \tag{71}$$

$$\begin{aligned}
A_2 &= U A_2 \int_0^{t/\varepsilon} \exp\left[\frac{G^\varepsilon(t, r) - G^\varepsilon(t - \varepsilon s, r)}{\varepsilon}\right] \left[1 - \frac{A_1 + A_2}{K} \exp\left(-\frac{G^\varepsilon}{\varepsilon}\right)\right] e^{-\beta_2 s} ds \\
&\quad + \beta_1 A_1 \int_0^{t/\varepsilon} \exp\left[\frac{G^\varepsilon(t, r) - G^\varepsilon(t - \varepsilon s, r)}{\varepsilon}\right] e^{-\beta_2 s} ds.
\end{aligned} \tag{72}$$

Taking the limit $\varepsilon \rightarrow 0$ we have

$$\begin{aligned}
A_1 &= A_1 \int_0^\infty e^{\frac{\partial G}{\partial t} s} \psi(s)e^{-\beta_1 s} ds + A_1 < r > \frac{\partial G}{\partial r} \int_0^\infty e^{\frac{\partial G}{\partial t} s} \psi(s)e^{-\beta_1 s} ds \\
&\quad + \frac{\sigma^2 A_1}{2d} \left(\frac{\partial G}{\partial r}\right)^2 \int_0^\infty e^{\frac{\partial G}{\partial t} s} \psi(s)e^{-\beta_1 s} ds + \beta_2 A_2 \int_0^\infty e^{\frac{\partial G}{\partial t} s} \Psi(s)e^{-\beta_1 s} ds,
\end{aligned} \tag{73}$$

$$A_2 = U A_2 \int_0^\infty e^{\frac{\partial G}{\partial t} s} e^{-\beta_2 s} ds + \beta_1 A_1 \int_0^\infty e^{\frac{\partial G}{\partial t} s} e^{-\beta_2 s} ds. \tag{74}$$

Then Eqs.(73) and (74) can be rewritten as a system of linear equations for A_1 and A_2

$$\begin{aligned}
&A_1 \left[1 - \left(1 + < r > \frac{\partial G}{\partial r} + \frac{\sigma^2}{2d} \left(\frac{\partial G}{\partial r}\right)^2 \right) \int_0^\infty e^{\frac{\partial G}{\partial t} s} \psi(s)e^{-\beta_1 s} ds \right] \\
&- A_2 \beta_2 \int_0^\infty e^{\frac{\partial G}{\partial t} s} \Psi(s)e^{-\beta_1 s} ds = 0,
\end{aligned} \tag{75}$$

$$A_1\beta_1 \int_0^\infty e^{\frac{\partial G}{\partial t}s} e^{-\beta_2 s} ds - A_2 \left[1 - U \int_0^\infty e^{\frac{\partial G}{\partial t}s} e^{-\beta_2 s} ds \right] = 0. \quad (76)$$

This system has a non-trivial solution when the corresponding determinant is equal to zero:

$$\begin{aligned} & \left[1 - \left(1 + < r > \frac{\partial G}{\partial r} + \frac{\sigma^2}{2d} \left(\frac{\partial G}{\partial r} \right)^2 \right) \int_0^\infty e^{\frac{\partial G}{\partial t}s} \psi(s) e^{-\beta_1 s} ds \right] \left[1 - U \int_0^\infty e^{\frac{\partial G}{\partial t}s} e^{-\beta_2 s} ds \right] \\ & - \beta_1 \beta_2 \int_0^\infty e^{\frac{\partial G}{\partial t}s} \Psi(s) e^{-\beta_1 s} ds \times \int_0^\infty e^{\frac{\partial G}{\partial t}s} e^{-\beta_2 s} ds = 0. \end{aligned} \quad (77)$$

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